

### III. REMARKS

#### Preliminary Remarks

Reconsideration and allowance of the present application based on the foregoing amendment and following remarks are respectfully requested. Claims 16-27 are currently pending and at issue in this application. This response is timely filed. The applicants request entry of the foregoing amendment, as it will either place the application in condition for allowance or place the application in better form for appeal.

The applicants wish to thank the examiner for discussing the outstanding issues in this application on March 8, 2005.

New claim 28 is directed to a method for production of L-tryptophan, L-phenylalanine, or L-tyrosine, comprising (a) fermenting an *E. coli* host cell that contains an isolated polynucleotide selected from the group consisting of (i) a nucleotide sequence as set forth in SEQ ID NO: 1; and (ii) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2; (b) expressing an *Arthrobacter aureescens*' L-N-carbamoylase from step (a); and (c) contacting the L-N carbamoylase of step (b) with N-carbamoyl or N-formyl amino acids to produce L-tryptophan, L-phenylalanine, or L-tyrosine. Support for new claim 28 can be found throughout the specification, for example, at Table 1 on page 18.

Dependent claims 29-33 are ultimately dependent upon claim 28 and thus contain the same essential steps for the method for production of L-tryptophan, L-phenylalanine, or L-tyrosine using *Arthrobacter aureescens*' *hyuC* gene as set forth in SEQ ID NO: 1. Support for dependent claims 29-33 can be found throughout the specification, for example, on page 5, lines 21-23 and page 17, lines 12-20.

New claim 34 is directed to a method for production of L-thienylalanine comprising (a) fermenting an *E. coli* host cell that contains an isolated polynucleotide selected from the group consisting of (i) a nucleotide sequence as set forth in SEQ ID NO: 1; and (ii) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2; (b) expressing an *Arthrobacter aureescens*' L-N-carbamoylase from step (a); and (c) contacting the L-N carbamoylase of step (b) with N-carbamoyl-L-thienylalanine to produce L-thienylalanine. Support for new claim 34 can be found throughout the specification, for example, at Table 1 on page 18. Dependent claims 29-33 are ultimately dependent upon claim 28 and thus contain the same essential steps for the method for production of L-tryptophan, L-phenylalanine, or L-tyrosine using *Arthrobacter aureescens*' *hyuC* gene as set forth in SEQ ID

Altenbuchner *et al.* U.S. Patent Appl. No. 10/045,063

NO: 1. Support for dependent claims 29-33 can be found throughout the specification, for example, on page 5, lines 21-23 and page 17, lines 12-20.

On page 2 of the official action, the examiner objected to the specification because the description for Figure 2 does not match the description provided to Figure 2. The applicants have amended the brief description of the Figure 2 on page 6 of the specification. Specifically, the applicants have discussed the stability of the N-L-carbamoylase enzyme activity over 100 hours (from hour 40 to 140) at 37°C and believe this discussion matches the description provided regarding the description of Figure 2 in the specification. Support for the amendment can be found throughout the specification, for example, on page 4, lines 17-22. In view of the foregoing amendment and remark, the applicants respectfully submit that the objection to the brief description of Figure 2 has been overcome and should be withdrawn.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in a continuing application.

#### **Patentability Remarks**

##### **Rejection Under 35 U.S.C. §112. Second Paragraph**

On page 3 of the official action, the examiner rejected claims 22-27 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. Specifically, the examiner alleged that claim 22 is confusing because it is drawn to a method for producing L-methionine by contacting the *Arthrobacter aureescens* L-N carbamoylase with N-carbamoyl-L-thienylalanine.

Amended claim 22 is now directed to a method for production of L-methionine comprising (a) fermenting an *E. coli* host cell that contains an isolated polynucleotide selected from the group consisting of (i) a nucleotide sequence as set forth in SEQ ID NO: 1; and (ii) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2; (b) expressing an *Arthrobacter aureescens* L-N-carbamoylase from step (a); and (c) contacting the L-N carbamoylase of step (b) with N-carbamoyl-L-methionine to produce L-methionine. Support for amended claim 22 can be found throughout the specification, for example, Table 2 on page 18. The applicants submit that claim 22 is no longer confusing as the method for producing L-methionine requires *Arthrobacter aureescens* L-N carbamoylase to react with N-

Altenbuchner *et al.* U.S. Patent Appl. No. 10/045,063

carbamoyl-L-methionine instead of N-carbamoyl-L-thienylalanine. Claims 23-27 are ultimately dependent upon claim 22 and thus contain the same essential steps for the method of production of L-methionine using the *Arthrobacter aureescens*' *hyuC* gene as set forth in SEQ ID NO: 1.

In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of claims 22-27 under 35 U.S.C. §112, second paragraph, for being indefinite, has been overcome and should be withdrawn.

**Rejection Under 35 U.S.C. §112, First Paragraph, Enablement**

**Claims 22-27**

On pages 7 and 8 of the official action, the examiner rejected claims 22-27 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the examiner asserted that while the specification sufficiently describes a method of making L-methionine by contacting the substrate N-carbamoyl-L-methionine with the carbamoylase enzyme; or L-thienylalanine by contacting the substrate N-carbamoyl-L-thienylalanine with the same enzyme, the specification does not enable the production of L-methionine by contacting the substrate with N-carbamoyl-L-thienylalanine and the enzyme.

As discussed above, amended claim 22 is now directed to a method of making L-methionine by contacting the substrate N-carbamoyl-L-methionine with the *A. aureescens*' carbamoylase enzyme. Furthermore, new claim 34 is directed to a method of making L-thienylalanine by contacting the substrate N-carbamoyl-L-thienylalanine with the *A. aureescens*' carbamoylase enzyme. As acknowledged by the examiner, both of these methods are enabled by the specification. As discussed above, dependent claims 23-27 and 35-39 contain the same essential steps as either independent claim 22 and claim 34 and are thus enabled as well. In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of claims 22-27 under 35 U.S.C. §112, second paragraph, has been overcome, and a similar rejection of new claims 34 and its dependents would be improper.

*Claims 16-21*

On pages 3-7 of the official action, the examiner rejected claims 16-21 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Specifically, the examiner asserted that while the specification was enabling for a method of producing L-amino acids such as L-tryptophan, L-phenylalanine, and L-tyrosine by using the specific L-N-carbamoylase isolated from *Arthrobacter aureescens* (having the amino acid sequence set forth in SEQ ID NO: 2), the specification is not enabling for a method of producing any or all L-amino acids. The examiner alleged that the specification teaches that the substrate spectrum and the stereospecificity of the isolated rec-L-N-carbamoylase isolated from *A. aureescens* is small producing only 3 natural aromatic L-amino acids (*i.e.*, L-tryptophan, L-phenylalanine, and L-tyrosine), but provides no guidance with regard to making all or any L-amino acid.

Amended claim 16 is directed to a method for production of a  $\beta$ -aryl-substituted L-amino acid or  $\beta$ -indole-substituted L-amino acid, comprising (a) fermenting an *E. coli* host cell that contains an isolated polynucleotide selected from the group consisting of (i) a nucleotide sequence as set forth in SEQ ID NO: 1 and (ii) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 2, (b) expressing an *Arthrobacter aureescens*' L-N-carbamoylase from step (a), and (c) contacting the L-N carbamoylase of step (b) with N-carbamoyl or N-formyl amino acids to produce a  $\beta$ -aryl-substituted L-amino acid or  $\beta$ -indole-substituted L-amino acid. Support for amended claim 16 can be found throughout the specification, for example, on page 3, lines 22-27 and Table 1.

In view of the foregoing amendment and remarks regarding amended claim 16, the applicants submit that undue experimentation would not be required to a method for production of a  $\beta$ -aryl-substituted L-amino acid or a  $\beta$ -indole-substituted L-amino acid by using *A. aureescens*' L-N-carbamoylase. Amended claim 16 satisfies the "how to make prong" of the enablement requirement because the scope of the claims is "reasonably correlated" with the teachings of the application (See MPEP §2164.04(b)). The present specification and the ordinary skill in the art permit one to use SEQ ID NO: 2 as a carbamoylase for producing  $\beta$ -aryl-substituted L-amino acid or a  $\beta$ -indole-substituted L-amino acid. Specifically, the phrase " $\beta$ -aryl-substituted L-amino acid" finds direct support in the specification on page 3, lines 22-25 wherein the specification teaches that the recombinant carbamoylases (*i.e.*, such those isolated from *Arthrobacter aureescens*) allow for

Altenbuchner *et al.* U.S. Patent Appl. No. 10/045,063

generation of  $\beta$ -aryl-substituted L-amino acids by means of their enzymatic conversion of (D,L)-N-carbamoyl amino acids.

The applicants further submit that the term " $\beta$ -indole-substituted L-amino acid" in amended claim 16 is inherently taught in the specification in Table 1. Specifically, L-tryptophan is inherently a  $\beta$ -indole-substituted L-amino acid. The L-amino acid tryptophan has an indole group located at the  $\beta$  position. Thus, one of skill in the art would recognize that the term  $\beta$ -indole-substituted L-amino acid is the necessarily present or defining chemical structure of L-tryptophan and would further recognize that the  $\beta$ -indole of tryptophan is not due to some probability or possibility. Accordingly, the application has sufficient written descriptive support for the term " $\beta$ -indole-substituted L-amino acid" as well due to the inherent chemical characteristics of L-tryptophan (see MPEP §2163.07(a) and *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999)). In addition, the disclosure on page 11, lines 11-21 and Table 1 teaches how the  $\beta$ -aryl-substituted L-amino acids or a  $\beta$ -indole-substituted L-amino acid are produced by the recombinantly expressed *A. aurescens* L,N-carbamoylase. Accordingly, it is the applicants' position that one of skill in the art would not require undue experimentation to identify specific  $\beta$ -aryl-substituted L-amino acids or a  $\beta$ -indole-substituted L-amino acid produced by the recombinantly expressed *A. aurescens* L,N-carbamoylase. Thus, due to the teachings of the specification and what was known in the art at the time of filing, the experimentation necessary to practice the present invention would not be undue.

Claim 17-21 are dependent upon claim 16 and thus draw the same limitations. In view of the foregoing amendment and remarks, the applicants respectfully submit that the rejection of claims 16-21 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement, has been overcome and should be withdrawn.


Altanbuchner *et al.* U.S. Patent Appl. No. 10/045,063

### III. CONCLUSION

In view of the foregoing, the applicants respectfully submit that this application is in condition for allowance. A timely notice to that effect is respectfully requested. If questions relating to patentability remain, the examiner is invited to contact the undersigned to discuss those questions.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP



Thomas A. Cawley, Jr., Ph.D.

Reg. No. 40,944

Tel. No. 703-905-2144

Fax No. 703-905-2500

TAC/PAJ  
P.O. Box 10500  
McLean, VA 22102  
(703) 905-2000